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☐ 1: Br J Cancer 1992 Sep;66(3):474-8

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A monoclonal antibody-beta-glucuronidase conjugate as activator of the prodrug epirubicin-glucuronide for specific treatment of cancer.

Haisma HJ, Boven E, van Muijen M, de Jong J, van der Vijgh WJ, Pinedo HM.

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Department of Medical Oncology, Free University Hospital, Amsterdam, The Netherlands.

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The anti-pan carcinoma monoclonal antibody (MAb) 323/A3, linked to E. coli-derived beta-glucuronidase (GUS) was used to study the tumour-site-selective activation of the prodrug Epirubicin-glucuronide (Epi-glu). Epi-glu was isolated from the urine of patients treated with Epirubicin (Epi) by reversed phase chromatography on a silica-C18 column. Epi-glu was stable in human blood and was not converted into Epi by A2780, MCF-7, or OVCAR-3 cancer cells, despite the presence of intracellular GUS. The stability of the prodrug was confirmed in BALB/c mice. MAb 323/A3 and GUS were linked through a stable thioether bond. The conjugate (1:1) was purified by ion exchange and gel filtration chromatography. Binding to target cells revealed an immunoreactivity of at least 60% and good retention of enzyme activity. A protein dye (sulforhodamine B) assay was used to analyse cytotoxicity. Epi (IC₅₀ of 0.003-0.2 microM) was 100-1,000 times more toxic than Epi-glu (IC₅₀ of greater than 20 microM), when cancer cells were exposed for 4 or 24 h to the drugs. The low cytotoxicity of Epi-glu was most likely due to the reduced cellular uptake rate of the prodrug (2.7 pmol 10⁻⁶ cells min⁻¹) as compared to that of the parent compound (25 pmol 10⁻⁶ cells min⁻¹). Pretreatment of antigen-positive cells with the 323/A3-GUS conjugate prior to prodrug exposure completely restored cytotoxicity as a result from hydrolysis of Epi-glu into Epi. Our results demonstrate that the 323/A3-GUS conjugate can specifically activate the stable non-toxic prodrug Epi-glu at the tumour cell level.

PMID: 1520585 [PubMed - indexed for MEDLINE]

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